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(54) Title: TREATMENT OF STEATOSIS USING HYPERTHERMIA

(57) Abstract: The invention provides a method for treating a patient having a level of steatosis comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to reduce the patient's level of steatosis by 30 percent or more six months after the core temperature has been raised and returned to normal at least one time.

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TREATMENT OF STEATOSIS USING HYPERTHERMIA

FIELD OF THE INVENTION

This invention relates to hyperthermic treatment of steatosis.

BACKGROUND OF THE INVENTION

Steatosis is an abnormal accumulation of fat in the liver. Microvesicular and macrovesicular forms relate to the vesicle size of fat in the liver. Steatosis can be prominent in alcoholic liver disease (alcoholic steatohepatitis), non-alcoholic steatohepatitis (NASH syndrome), hepatitis B or C infections, obesity, diabetes mellitus, malabsorption, use of steroids, and use of certain other drugs. When the accumulation of fat goes along with inflammation the condition is known as steatohepatitis. Overtime this condition can lead to liver fibrosis and/or cirrhosis.

Steatosis will cause elevations in liver enzymes and is diagnosed through imaging techniques like ultrasound, CT, MRI, and/or liver biopsy. Currently there is no proven effective therapy for NASH or other forms of steatosis. Management currently seeks to modify risk factors.

SUMMARY OF THE INVENTION

The invention provides a method for treating a patient having a level of steatosis comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time. The core temperature is raised to a temperature range and a duration sufficient to eliminate or reduce the patient's level of steatosis by 30 percent or more six months after the core temperature has been raised and returned to normal at least one time, and the patient's level of steatosis is determined at least once before the core temperature has been raised said at least one time.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method for treating a patient having a level of steatosis comprising raising the core temperature of the patient and then

returning the core temperature of the patient to normal at least one time. The core temperature is raised to a temperature range and a duration sufficient to reduce the patient's level of steatosis by 30 percent or more six months after the core temperature has been raised and returned to normal at least one time, and the patient's level of steatosis is determined at least once before the core temperature has been raised said at least one time.

"Returning the core temperature of the patient to normal" includes allowing the patient to cool through ambient heat loss and actively cooling the patient. In the examples described below, the patient is cooled by ambient heat loss and active cooling to a temperature of 39°C. The patient is released from the treatment center and the patient's temperature gradually returns to normal (37°C) over a period of a few days. In one embodiment, the core temperature of the patient is raised and returned to normal one time. In another embodiment, the core temperature of the patient is raised and returned to normal two or more times. In one embodiment, the core temperature is raised by circulating the patient's blood from the patient, through an extracorporeal blood flow circuit, and back to the patient, wherein the blood returned to the patient has been heated within the blood flow circuit to an elevated temperature range. The patient's blood can be circulated from the patient through a blood vessel and returned to the patient through a blood vessel. In one embodiment, the patient's blood is circulated from the patient through a vein and returned to the patient through a vein. In another embodiment, the patient's blood is circulated from the patient through an artery and returned to the patient through a vein. In another embodiment, the core temperature is raised by inserting a heating element into the patient and the heating element heats the patient's blood. The heating element can be inserted into a blood vessel of the patient.

The heating element can be inserted into a central vessel, i.e., aorta or vena cava, where it can heat the blood passing by and eventually heating the blood to such a degree that the net temperature gain exceeds the losses due to the normal (physiologic) cooling mechanisms. Over time the body temperature can be raised to a predetermined point and maintained for a predetermined time. The heating element can be housed within a sheath or catheter at one or multiple positions along its length. The sheath or catheter can contain wires, conduits, fiberoptic, or other materials to supply power to the heating element. External to the body there could be a plug to connect the sheath or catheter to the control

system. The sheath or catheter can be treated to give it antithrombogenic properties. This treatment can be chemical or a high energy corona or plasma discharge in the presence of a monomeric gas. The method of insertion can be through a cut-down or percutaneously (Seldinger Technique).

The heating element's method of heating can be by an electrical heating, radiofrequency, or laser. The heating element should not exceed 50°C at the surface that contacts blood. Such a heating element can be used for core heating and can also be used for local or regional heating. For example, a percutaneous insertion into an artery with a hollow sheath or catheter can be made to accommodate a steering guidewire so the device can be placed into the hepatic artery. A second hollow catheter with a thermistor tip can be placed, via a venous percutaneous stick, into the hepatic vein for liver temperature.

Methods which heat the blood to raise the core temperature, such as extracorporeal whole body hyperthermia, are preferred. However, methods in which the core temperature is raised by other methods such as by infrared radiation, convection, or surface contact such as a heating blanket can also be used in the method of the invention.

The core temperature can be raised to a temperature range of from 38 to 43°C, more preferably 41 to 42°C. The core temperature can be raised for a period of from 2 minutes to sixteen hours, a period of from one-half to three hours, a period of from one to two hours, or a period of from 100 to 140 minutes, or for 120 minutes. The core temperature can be taken rectally. For purposes of this application, the "core temperature" means rectal temperature. Temperatures other than the rectal temperature can be taken in the practice of the invention, e.g., esphogeal, bladder, tympanic, or cardiac line temperatures. The relationship between such other temperatures and the rectal temperature is well known in the art and such measurement by other methods will allow determination of the core temperature as defined herein.

Recommended exposure times during extracorporeal whole body hyperthermia are given in Table 1 below.

TABLE 1

Core Temperature (°C)	Exposure (minutes)
39	960
40	480
41	240
42	120
43	60

The patient's level of steatosis can be determined at least once before the core temperature has been raised at least one time; at least once after the core temperature has been raised and returned to normal at least one time; at least two different times after the core temperature has been raised and returned to normal at least one time, or combinations thereof.

In embodiments of the invention, the patient's level of steatosis is reduced by 30 percent or more six months after the core temperature has been raised and returned to normal at least one time, more preferably, by 50 percent or more, more preferably, by 75 percent or more, by 90 percent or more, or by 95 percent or more. In a preferred embodiment, the patient's level of steatosis is eliminated six months after the core temperature has been raised and returned to normal at least one time.

Steatosis is determined by liver biopsy to see if steatosis is present in the liver. In embodiments of the invention, the patient has macrovesicular steatosis, microvesicular steatosis, or both macrovesicular and microvesicular steatosis. The existence of macrovesicular steatosis can be established by a liver biopsy showing large fatty vesicles. Microvesicular steatosis can be established by a liver biopsy showing small fatty vesicles. Other methods such as ultrasound, MRI, CAT scan, and fluoroscopy can show the presence of steatosis, but these methods cannot be used to distinguish between macrovesicular and microvesicular steatosis using the technology available today. In a preferred embodiment, the patient has macrovesicular steatosis and the macrovesicular steatosis is eliminated six months after the core temperature has been raised and returned to normal said at least one time. In another preferred embodiment, the

patient has microvesicular steatosis and the microvesicular steatosis is eliminated six months after the core temperature has been raised and returned to normal said at least one time.

In embodiments of the invention, the patient is infected with hepatitis C virus; the patient is not infected with hepatitis C virus; the patient is infected with hepatitis B virus; and the patient is not infected with hepatitis B or C virus. In embodiments of the invention, the patient has steatohepatitis; the patient has non-alcoholic and non-viral steatohepatitis; the patient has viral steatohepatitis; and the patient has alcoholic steatohepatitis.

In embodiments of the invention, the patient is obese, the patient has diabetes mellitus, the patient has malabsorption, the patient has been exposed to steroids and/or the patient has been exposed to certain other drugs.

In embodiments of the invention, the patient's level of steatosis is reduced by 30 percent or more three months after the core temperature has been raised and returned to normal at least one time, more preferably, by 50 percent or more, by 75 percent or more, by 90 percent or more, or by 95 percent or more. In a preferred embodiment, the patient's level of steatosis is eliminated six months after the core temperature has been raised and returned to normal at least one time.

The method of the invention can further comprise treating the patient with a pharmaceutical indicated for hepatitis C. The efficacy of a pharmaceutical effective for treatment of HCV in some patients can be increased when combined with hyperthermia. The method of the invention can also comprise treating the patient with a pharmaceutical indicated for HCV where such pharmaceutical was not efficacious for stand alone treatment for HCV and when combined with hyperthermic treatment results in the pharmaceutical being efficacious in some patients. The patient can be treated with a single pharmaceutical effective against hepatitis C or with two or more pharmaceuticals effective against hepatitis C. The drug can be administered to the same patient at several points: before raising the core temperature of the patient at least one time, while the core temperature of the patient is raised, and after the core temperature of the patient has been raised and returned to normal at least one time, or combinations thereof.

The pharmaceutical can be selected from interferons, protease inhibitors, cytokines, or any combination of antiviral drugs. The pharmaceutical can be

selected from ribavirin, lamivudine, interferon alfacon-1, interferon alfa-2a, interferon alfa-2b, interferon-alfa-nl, thymosin alpha-1, interleukin-2, interferon alpha-n3, ketoprofen, interferon beta-la, interferon gamma-1b, interleukin-12, histamine dihydrochloride, thymalfasin, zidovudine, didanosine, zalcitabine, stavudine, abacavar, nevirapine, delaviridine, efavirenz, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, or combinations thereof. In a preferred embodiment, the pharmaceutical can be selected from an interferon, ribavirin, or lamivudine. In another preferred embodiment, the pharmaceutical is an alpha interferon. The pharmaceutical can also include antioxidants, non-steroidal anti-inflammatory drugs, cholic acids like ursodeoxycholic acid and/or reactive oxygen free radical scavengers. Several pharmaceuticals are being studied and some are available for treatment of hepatitis C. Commercially available interferons include INFERGEN (interferon alfacon-1, manufactured by Amgen Inc., Thousand Oaks, California), ROFERON-A, (interferon alfa-2a, manufactured by Roche Pharmaceuticals, Nutley, New Jersey), INTRON A (interferon alfa-2b, manufactured by Schering Corporation, Kenilworth, New Jersey), and WELLFERON (interferon alfa-nl, manufactured by Glaxo Wellcome Inc., Research Triangle Park, North Carolina). Ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboximide) in combination with INTRON-A is sold as REBETRON by Schering Corporation.

A patient infected with HCV might have an acute HCV infection or a chronic HCV infection. The patient might be co-infected with a pathogen. The pathogen might be a virus, a spirochete, or a bacterium. The virus might be a heat labile virus. The heat labile virus might be selected from herpesviruses, hepadnaviruses, togaviruses, flaviviruses, coronaviruses, rhabdoviruses, filoviruses, paramyxoviruses, othomyxoviruses, bunyaviruses, arenaviruses, or retroviruses. The heat labile virus might be HIV, hepatitis B virus, Ebstein-Barr virus, cytomegalovirus, or varicella-zoster virus. In a preferred embodiment, the heat labile virus is HIV. The spirochete might be from the genus treponema, borrelia, or leptospira. The spirochete might be *Treponema pallidum, Treponema pertenue, Treponema carateum, Treponema pallidum endemicum, Borrelia burgdorferi, Borrelia hermsii,* or *Leptospira interrogans*. The bacterium might be an aerobic or anaerobic bacterium.

The method of the invention can further comprise treating the patient with a pharmaceutical indicated for steatohepatitis. The efficacy of a pharmaceutical effective for treatment of steatohepatitis in some patients can be increased when combined with hyperthermia. The method of the invention can also comprise treating the patient with a pharmaceutical indicated for steatohepatitis where such pharmaceutical was not efficacious for stand alone treatment for steatohepatitis and when combined with hyperthermic treatment results in the pharmaceutical being efficacious in some patients. The patient can be treated with a single pharmaceutical effective against steatohepatitis or with two or more pharmaceuticals effective against steatohepatitis. The drug can be administered to the same patient at several points: before raising the core temperature of the patient at least one time, while the core temperature of the patient is raised, and after the core temperature of the patient has been raised and returned to normal at least one time, or combinations thereof.

The pharmaceutical can be selected from cholic acids such as ursodeoxycholic acid, vitamin E, metformin, and betaine.

The invention also provides a method for treating a patient having a level of steatosis comprising raising the temperature of the patient's liver and then returning the temperature of the patient's liver to normal at least one time. The temperature of the patient's liver is raised to a temperature range and a duration sufficient to eliminate or reduce the patient's level of steatosis by 30 percent or more six months after the temperature of the patient's liver has been raised and returned to normal at least one time, and the patient's level of steatosis is determined at least once before the temperature of the patient's liver has been raised said at least one time.

In embodiments of the invention, the temperature of the liver is raised by local, regional, or intraperitoneal hyperthermia. In addition, the liver can be heated by the methods for raising the core temperature that are described herein.

Conventional hyperthermia equipment can be used in the methods of the invention.

EXAMPLES

Twelve patients with chronic hepatitis C virus infection, genotype 1 and previous non-response to interferon mono- or combination therapy were treated. The patients received a single session of Extracorporeal Whole Body

Hyperthermia (EWBH). The patients continued HCV drug treatment until the hyperthermia treatment and then discontinued their drug treatment. All patients had no more than Child Pugh A score for liver function.

Treatment consisted of one single session of EWBH with the core temperature raised to 41.8° ± 0.15°C for 120 minutes. The device used is based on a small volume extracorporeal veno-venous circulation through a heater-cooler system (Temet™, First Circle Medical, Minneapolis, MN, USA).

Preliminary results show that EWBH induces both HCV-specific and general T-cell immunity, combined with lowering the viral load.

All patients underwent a liver biopsy before treatment and so far nine patients have had their 24 weeks post-treatment liver biopsy. Inflammatory grading, fibrosis staging and steatosis were evaluated according to various scoring systems.

Pre-treatment biopsies revealed steatosis in 50% (6/12) of the patients. The results of the biopsies are shown in Table 2 below. Steatosis was macrovesicular only in one, microvesicular only in one, and mixed macrovesicular and microvesicular in four. The steatosis was classified as macrovesicular or microvesicular based on histological appearance. A liver biopsy is taken, the tissue is fixed in formalin and cut to slices which are stained and subsequently read under a microscope. If steatosis (fat) is present, it is characterized as macrovesicular and/or microvesicular steatosis. Each type is quantified by counting the steatotic cells as a percentage of the total number of liver cells in the same area. The scoring code used was: score 0: no steatosis; score 1: mild steatosis, < 5%; score 2: moderate steatosis, 5-30%; score 3: severe steatosis: > 30%.

A 30 percent reduction in steatosis would occur, for example, if the total number of steatotic cells (macrovesicular and microvesicular) declined by 30 percent (e.g., 30 percent down to 21 percent).

After hyperthermia treatment, the level of steatosis was reduced in all six patients. One patient who had not previously exhibited steatosis developed steatosis.

TABLE 2

Visit		Steatosis	Micro	Macro
1	Screen	Pre	0	0
	24-Week	Post	0	0
2	Screen	Pre	0	0
	24-Week	Post	0	0
3	Screen	Pre	1	1
	24-Week	Post	0	0
4	Screen	Pre	0	0
	24-Week	Post	0	0
5	Screen	Pre	2	2
	24-Week	Post	1	0
6	Screen	Pre	1	0
	24-Week	Post	0	1
7	Screen	Pre	0	0
	24-Week	Post	1	1
8	Screen	Pre	3	2
	24-Week	Post	2	1
9	Screen	Pre	0	1
	24-Week	Post	0	0
10	Screen	Pre	1	1
	24-Week	Post	1	0
11	Screen	Pre	0	0
	24-Week	Post	0	0
12	Screen	Pre	0	0
	24-Week	Post	na	na

The details of the clinical protocol followed for patients and the equipment used are presented below.

Clinical Protocol

I. Synopsis

This is an open label pilot study in chronic hepatitis C patients, genotype 1, in which the safety and early effect on viral load of Extracorporeal Whole Body Hyperthermia (EWBH) will be recorded. Patients will be treated with one session of EWBH. Follow-up is completed at week 24. Fifteen patients will be included.

II. Study hypotheses

- Patients with HCV infections can be safely treated with EWBH
- Patients treated with EWBH have lower Hepatitis C viral load values at various individual time intervals, during the first 24 weeks after EWBH than during the last 24 weeks before EWBH.
- Patients treated with EWBH have higher mean quality-of-life scores at various individual times after EWBH than pre EWBH.

III. Study objectives

The purpose of this investigation is to assess the safety and early effect on viral load of EWBH treatment over 24 weeks in individuals with chronic HCV infection, Genotypes 1.

The study is an open label pilot study in a single centre.

IV. Patient definition

Fifteen patients with chronic hepatitis C, genotype 1a or 1b, will be enrolled in this study. Enlisted will be patients non-responding to or relapsers from previous interferon alpha monotherapy or combination therapy (with ribavirin and/or amantadine), patients who were intolerant of interferon alpha therapy and those who refused drug treatment. Chronic hepatitis C is defined as: positive antibodies to HCV, positive serum HCV RNA and elevated transaminases at least once in the previous 6 months. Patients will be identified, screened and enrolled under supervision of Dr. J. van Hattum, Chief of the Department of Hepatology of the UMC (Utrecht, the Netherlands).

All patients must meet the entrance screening, described in VII. Patient Selection Criteria.

V. Treatment scheme

The patients will undergo a single session of EWBH treatment, with their core temperature raised to 41.80°C ± 0.20°C for 120 minutes.

VI. Patient selection criteria

A. Inclusion criteria:

- Obtained written informed consent
- Positive serum HCV RNA (>100,000 copies/ml)
- Age between 18 and 65 years
- Is a non-responder to or relapser from, has proved intolerance of, or refused interferon alpha monotherapy or combination therapy (with ribavirin and/or amantadine).
- Child Pugh score A (appendix 4)
- Normal ECG.
- Echocardiogram with EF > 45%, normal LV function and no history of coronary artery diseases (appendix 5).
- Karnofsky Performance status: ≥70%. (appendix 6)
- Granulocyte Count ≥ $1,5x10^9$/L (grade 1 appendix 7)
- White Blood Count (WBC) ≥ $3,0x10^9$/L (grade 1 appendix 7)
- Platelet Count ≥ $50x10^9$/L (grade 2 appendix 7)
- Hematocrit ≥ 0,35 L/L
- Hemoglobin ≥ 5,8 mmol/L (grade 1 appendix 7)
- Serum creatinine ≤ 150 μmol/L
- Abnormal ASAT and/or ALAT at least once in the previous 6 months.
- Negative pregnancy test for females.
- Forced Expiratory Volume (FEV1) > 60 % of expected function, vital capacity (VC) ≥ 70% of expected function.
- No signs of vascular problems and/or tumors on the MRI scan of the brain.
- Negative ELISA test for HIV.
- Intention to be treated and participate treatment

B. Exclusion criteria:

- Child Pugh score B or C (appendix 4).
- History of decompensated liver cirrhosis, jaundice, esophageal varices, gastrointestinal hemorrhage or abdominal ascites within the last 12 months.
- Major other liver disease with or without portal hypertension.
- Patients with HCV genotypes non-1.
- New York Heart Association (NYHA) classification II, III or IV (appendix 5).
- History of a myocardial infarction, abnormal stress test suggesting ischemic changes, malignant, uncontrollable arrhythmias or documented unstable angina within the last 12 months.
- Major surgery within four weeks of protocol therapy.
- History of central nervous hemorrhage.
- Known hypersensitivity, allergic history to heparin, protamine, pork/beef products, fish, lidocaine or other anesthetic agents.
- Consistent systolic BP > 160 and/or consistent diastolic BP > 105.
- Use of non-steroidal anti-inflammatory drugs (NSAIDs) during the last two weeks.
- Currently being treated with interferon monotherapy or in combination with ribavirin/amantadine.
- Patients with current malignancy.
- History of treatment with chemotherapy for malignancy within the last 5 years with the exception of localized basal or squamous cell carcinoma of the skin.
- Any type of uncontrolled medication abuse.
- Drug or alcohol abuse within the 6 months.
- Subjects who have had liver, kidney or heart transplants.
- Depression as defined by (1) a major depression episode requiring medication,

hospitalization or electroconvulsive treatment; (2) any history of suicidal ideation; (3) history of severe psychiatric disorders or other psychiatric disorder which in the opinion of the investigator might be exacerbated by the use of EWBH.

- Currently enrolled in any other investigational clinical trial excludes participation in this protocol.

- Any condition which in the opinion of the (co)-investigator might interfere with the safety of the patient or evaluation of the study objectives.
- Patients with haemophilia or other bleeding tendency.

VII. Screening

After obtaining the informed consent the patients will undergo a complete medical history, physical examination and laboratory check according to the flowchart (appendix 8). Preferably all patients will have a liver biopsy before starting the EWBH. Once a patient has fulfilled all screening criteria, the investigator will document the eligibility on the study data forms. The investigator shall then document on the study data forms the patient ID and the patient will be treated according to protocol.

VIII. EWBH treatment

A. Pre procedure:

After the history, physical examination, laboratory procedure has been completed and entry criteria satisfied, the patient will be admitted to the hospital on the day before or on the day of the procedure. Blood will be drawn according to the table of required observations (appendix 9). Patient must be non-per os (NPO) for at least 6 hours prior to the procedure. Prophylactic antibiotics (the standard for vascular procedures) will be given, starting 2 hours prior to procedure and will be continued for 24 hours.

B. Procedural Parameters:

1. Description of Treatment Facility:

The OR or treatment room that is used for the procedure does not have to be modified for this procedure. Operating table shall be equipped with a foam rubber mattress and/or pads for flexor point protection. Arms will be placed at 70° sideway position.

2. Patient Instrumentation for EWBH:

The following shall be placed in the Operating Room prior to EWBH:

I. Peripheral intravenous line (one)

II. Central intravenous line in internal jugular or subclavian vein (triple lumen catheter)

III. Jugular Bulb catheter

IV. (Radial) artery cannula (invasive blood pressure measurement and sampling site)

V. Blood pressure device (sphygomomanometer)

VI. Ventilatory equipment

VII. ECG equipment (lead V5)

VIII. EEG equipment (2 channel)

IX. Non-invasive transcranial Doppler flow measurement equipment

X. Pulse Oximeter

XI. Rectal temperature probe*

XII. Esophageal temperature probe (general anesthesia)*

XIII. Tympanic temperature probe*

XIV. Urinary bladder catheter with thermistor (optional)

XV. Bilateral femoral venous catheters will be placed and connected to the hyperthermia unit

- *Temperature probes (rectal, esophageal and tympanic) must be certified to have been calibrated within 0.1°C to a NIST traceable device.*

3. Anesthesia:

General anesthesia is preferred for patient's comfort, mainly to prevent hyperactivity and/or restlessness during hyperthermia. Medication to ensure patient's comfort and safety as well as fluid replacement during the procedure will be administered at the discretion of the anesthesist.

If platelet counts during screening were under 100 x 10^9/L, patients will receive transfusion for correction of thrombocyte counts to above 100 x 10^9/L early during the procedure.

I. Volume replacement

Volume lost due to heat, evaporation and vasodilatation will be replaced: 0.5 L per 1 ^{0} C temperature increase. Thus, from 37 ^{0} C to 42 ^{0} C: 2.5 L fluid on top of 2.5 L daily requirement. About 1.5 L will be replaced via plasma expanders (Elohaes 6% or Gelofusine) and 3.5 L via Ringerlactate/Glucose 5% solutions.

II. Medication

The following medication will be used in order to obtain general anaesthesia:

- Rocuronium (muscle relaxans)
- Fentanyl (analgesic)
- Thiopental or propofol (hypnotics)
- Isoflurane (inhalatic anesthetic)
- Oxygen in air (FiO_2 0.35)

The following medication might be used to maintain hemodynamic stability:

- Ephedrine
- Phenylepinephrine
- Dopamine

C. EWBH conduct:

1. All parameters must be entered on case report forms:

Each patient will be continuously monitored for temperature during the procedure. Temperatures will be recorded in the CRF every 10 minutes throughout the procedure. The perfusionist will record all perfusion data in the CRF. Other patient's parameters will be recorded on standard O.R. (operating room) flow sheets.

2. Temperatures monitored:

1. Rectal (T_R)
2. Esophageal (T_E)
3. Blood outlet/Heat Exchanger (T_{Bld})
4. Water Bath (T_W)
5. Jugular Bulb (T_{BJ})

Optional:

6. Tympanic (T_T)
7. Bladder (T_U)
8. Pulmonary artery (T_{PA})

3. Preparation:

The perfusionist should prime the circuit with a balanced electrolyte, isotonic solution, and circulate until totally de-aired. The femoral veins will be cannulated using open or percutaneous methods for connection with the extracorporeal circuit.

A predetermined dose of heparin required for extracorporeal circulatory bypass will be calculated at 2 mg/kg in 1 dose with an ACT (Active Clotting Time) determination before and after the dose.

An ACT of more than 350 will be maintained during EWBH. Further doses of heparin, if needed, will be administered according to ACT measurement.

4. Heating phase:

I. EWBH shall be initiated at a blood flow rate of approximately 500 mL/min. The water circulating through the heat exchanger shall not exceed 49°C.

II. When either T_E or T_R (whichever is greater) reaches 41.60°C the plateau phase will begin. The time to reach a core temperature of 41.60°C is generally not less than 60 minutes.

5. Plateau phase:

I. The target thermal dose for each EWBH treatment is 41.80°C ± 0.20°C for 120 minutes ± 10 minutes. Every attempt will be made to deliver this dose to the patient.

II. When either T_E or T_R (whichever is greater) reaches 41.60°C the plateau phase begins. The target temperature for the plateau phase is 41.80°C and efforts should be made to achieve and maintain that temperature. T_W will be adjusted so that neither T_E nor T_R and T_{BJ} exceeds 42.00°C nor drops below 41.60°C. Temperature excursions above or below the target temperature range of 41.80°C ± 0.20°C will be allowed if the total time of the excursions is 10 minutes or less.

III. Cooling measures will be begin no later than 120 minutes after the start of the plateau phase. Because patients' thermal mass varies and therefore their rate of cooling, temperatures above 41.60°C may occur for up to 10 minutes after cooling measures begin.

6. Cooling phase:

Anticipated time to reach 39.00°C is 30-45 minutes.

I. Cooling will be initiated by resetting the thermostat of the TEMET to 35°C.

II. When T_E reaches 39°C, bypass will be discontinued.

III. De-cannulate and reverse heparin with protamine sulfate.

7. Once stable, the patient is transferred to the ICU

D. Post-EWBH :

n.b. These patients are to be considered "non-teaching patients". House staff must be under direction of attending staff.

1. Patient Monitoring in the ICU:

- Continuous ECG monitoring
- 12 lead ECG strip if indicated
- Temperature, pulse, respirations and blood pressures (every 15 minutes for the first ninety minutes, then every thirty minutes for the next ninety minutes)
- Urinary output

2. Medication

In cases of agitation, hyperactivity, sleeplessness, and/or restlessness following treatment with EWBH, mannitol, benzodiazepine sedatives or haldol are to be utilized with caution, administered only by members of the hyperthermia team.

The following protocol for administration of these medications will be followed:

- All discretionary medications are to be reviewed and approved by an attending physician from the hyperthermia team prior to being administered.
- No medical or surgical resident will write any medication orders of patients treated with EWBH without prior authorization from members of the hyperthermia team.

- At least one physician member of the hyperthermia team will evaluate the patient at every two-hour interval, or more frequently if indicated, for the initial four hours in the ICU.

E. Discharge:

Patients may be discharged from the hospital not within 12 hours after treatment neither before 24 hours after admission to the hospital. At time of discharge from the hospital, a CXR will be obtained to rule out the presence of pulmonary problems such as pneumothorax, atelectasis, or edema. At the time of discharge from the hospital, patients will be educated regarding precautions for administration of hepatically metabolized medications. After discharge from the hospital, it will again be emphasized that all discretionary medications are to be reviewed and authorized by the a physician member of the hyperthermia team prior to prescribing and administering to any patient treated with EWBH, including medications ordered by patient's private physician.

IX. Aftercare up to 4 weeks

- Should it become medically necessary to prescribe Benzodiazepine or Acetaminophen-containing medication in the 4-week period following EWBH:

- Liver function tests (LFTs) e.g. including, but not limited to, AST, ALT, alkaline phosphatase, total and direct and indirect bilirubin, must be drawn and analyzed immediately prior to prescribing and administering the medication. Whenever possible, avoid prescribing and administering any benzodiazepine or acetominophen-containing medication if any LFT is considered Grade 3 or 4 toxicity (appendix 7).
- Liver function tests (LFTs) e.g. including, but not limited to, AST, ALT, alkaline phosphatase, total and direct and indirect bilirubin must be drawn and analyzed within 72 hours and once weekly after prescribing and administering the medication. If any LFT rises to a Grade 3 or Grade 4 toxicity following administration of any medication in the 4-week period following EWBH, immediate discontinuation of the suspect medication is indicated with liver function tests repeated 24 hours later and followed to resolution (appendix 7).

X. Follow-up

All patients will be followed for 24 weeks after EWBH, without other treatment. Follow-up visits will be required weekly till week 4 and at week 8 (± 7 days), week 12 (± 7 days), week 16 (± 7 days), week 20 (± 7 days) and week 24 (± 7 days) after the EWBH treatment. On these dates subjective and objective data will be collected according to the flowchart. (appendix 8). All adverse events will be monitored and recorded in the CRF. Preferably all patients will have a second liver biopsy at the end of the 24-week trial period.

XI. Storage of blood samples

Blood samples for immunological determinations will be stored anonymously in a central laboratory. Only members of the hyperthermia team are allowed to use them. Blood will be tested for cytokines and cellular immunity if an effect of the EWBH treatment on viral load has been proven.

XII. Adverse effects and toxicity

Known side effects are restlessness, disturbances of sleep, sensitivity to hot baths, intermittent fever, dry skin, paresthesias in hands and feet, nausea, vomiting and facial edema. They are short-term and selflimited.

Pain is a possible side effect which can be caused by several aspects of the procedure: placement of the intravenous lines, obtaining of blood specimens, placements of the Foley catheter, the placement of the tube in the trachea, and placement of the temperature probes. Any pain due to these sources is generally self-limited.

Thrombopenia may occur during the EWBH.

Rarely there are side effects involving the circulatory system including heart failure, myocardial infarction, TIA and stroke.

If the patient is prone to Herpes Simplex, the heat treatment may cause an outbreak.

Allergy to one or more of the medications used (e.g. protamine sulphate) is possible and can cause itching, rash, dyspnea, hypotension and fainting. Infections due to the procedure are possible but unlikely.

XIII. Recording adverse events

All symptoms reported during the conduct of the protocol or follow up period will be recorded on the case report forms. Any adverse event of Grade 3-4 significance (appendix 7) will be reported on the Adverse Event Case Report Forms. Grade 4 adverse events will be reported by phone and FAX within 24 hours to the study sponsor. The Sponsor must receive a completed adverse event form within 5 days from the time that the principal investigator first learned of the event.

XIV. End points

Primary endpoints:

- Absence of side effects grade 4
- Viral load will be reduced by 90% of baseline value
- There will be an improvement in quality of life after EWBH

Secondary endpoints:

- Absence of side effects grade 3
- Undetectable HCV-RNA (< 600 IU/ml) at end of study

XV. Informed consent

Details of the study will be explained to each patient by the (co-) investigators and by use of a patient information sheet (appendix 10). Inclusion in the study can only take place after given written informed consent.

XVI. Withdrawal

Patients may voluntarily withdraw from the study at any time. Patients may be withdrawn from the study by their physician at any time. The reason for withdrawal has to be recorded in the Case Report Form provided for documentation of patient withdrawal. If the patient elects to pursue non-protocol therapy, every effort (e.g. phone calls, registered letters, etc.) will be made to obtain a final assessment of disease status, laboratory assessments and toxicity grading prior to the patient's departure from the study. If patients are lost-to-follow-up, all efforts will be made to locate the individual and follow the patient for safety and disease status during the remaining protocol follow-up period. In the case of a patient voluntarily withdrawing or being lost-to-follow-up within the first 8 weeks of the post-EWBH period, another patient as per protocol will be recruited.

Ancillary Protocol, Immunology

Background

A pilot study on the safety and therapeutic effect of whole body hyperthermia in 10-15 patients with hepatitis C infection will be performed in the University Medical Center in Utrecht. The study will be an open, single center study on chronic hepatitis C patients who have either not responded to previous therapy with Interferon-α (IFN-α), with or without ribavirin, or for whom treatment was not feasible. Only patients with genotype 1 (a or b) will be included.

Animal studies have shown that hyperthermia is a relatively safe procedure which has an effect on immunologic processes as well as tumour growth. Furthermore, the hemodynamic and cardiac effects of hyperthermia are being extensively studied in animals as well as in humans. In humans, whole body hyperthermia is already being used to treat cancer (1). The therapeutic effect of hyperthermia is mainly thought to be due to the release of cytokines, especially TNF-α, Interleukin-1 (IL-1) and IL-6, after the hyperthermia treatment (2,3).

The mechanism of whole body hyperthermal treatment of viral infections is not known. However, the antiviral effect against hepatitis C (HCV) was established in a patient with HIV-HCV coinfection. It was shown that the HCV viral load initially increased in the days following the hyperthermia, and then subsequently decreased to the pre-treatment level after one month. In the ensuing months, the HCV viral load became negative (personal communications, First Circle Medical). At present, there are 2 other studies being carried out on the effect of extra-corporeal whole body hyperthermia on patients with chronic HCV infection. These studies mainly focus on the safety aspect of hyperthermia.

One of the major problems concerning the current treatment of hepatitis C infection with Interferon and ribavirin is that the number of patients relapsing after treatment is high; this may be up to 60% in the 12 months after treatment has stopped. The number of relapses after hyperthermia treatment is not yet known, as this will require follow-up of the patients for at least one year.

Rationale of the ancilliary study to the protocol

The antiviral mechanism of whole body hyperthermia is not known. Two possible mechanisms may cause the antiviral effect:

1. Hyperthermia causes the release of a scala of chemokines from leukocytes and other cells, including antiviral interferons, interleukins and complement factors. The outburst cytokines at febrile temperatures might trigger the early activation of the host's defences. These chemokines may act anti-virally in several ways; by lysis of infected cells (TNF-∀, interferon-∀ and -(, IL-6, IL-10, which might explain the increase in the viral load in serum or plasma) and indirectly by stimulating the specific immune response to the hepatitis C virus (IL-1∀ and ∃, IL-2, interferon-().
2. Hyperthermia induces an increased expression of viral antigens and a release of virus from the hepatocytes and other cells that are infected (eg. Leukocytes). This increase of viral antigens, present on the cell surface and free in the serum, induces an increase in the immune reactions to the virus. This causes an increase of cytokines, which activate the specific immune response.

In both mechanisms the increase of viral load in plasma will be accompanied by an increase in both immune activity and cytokine release.

The mechanisms postulated above include massive immune activity in the 2 to 3 months following hyperthermia as well as a release of the virus, which may cause further damage to the liver. To monitor this, it is necessary to perform immunohistochemistry on two biopsies: one prestudy and one 6 to 12 months after the treatment (to detect possible irreversible liver damage).

The same biopsies can also be used to investigate the persistence of the virus in liver cells by performing HCV-specific hybridisation on the biopsies as well as HCV-PCR.

This may also establish whether the liver acts a reservoir for HCV (even when there is a negative viral load in plasma) thus enabling a relapse to be predicted.

Aim

1. To study the effect of hyperthermia on the hepatitis C virus dynamics in the first three months after treatment.
2. To compare several immune parameters during hyperthermia with the situation at normal body temperature.

3. To study the cytokine-changes and changes in HCV-specific cellular immunity in the period after hyperthermal treatment, in relation to the HCV viral load. This may give us some insight to unravel the mechanism of anti-viral action induced by the treatment.
4. To study the changes in the liver (by means of a liver biopsy) induced by the hyperthermia as this may also aid us a to fathom the mechanism of hyperthermia as well as predicting the chance of relapsing.

Aim 3 and 4 only apply if there seems to be an anti-viral effect documented with quantitative HCV PCR (aim 1), i.e. at least a 10-fold decrease in HCV PCR during the 6 months follow-up. Levels of cytokines, aim 2, however, will be measured anyway to document the influence of hyperthermia on their release.

Methods

For documentation of the viral dynamics, a quantitative HCV PCR (Roche Monitor or Taqman PCR) will be performed according to the following schedule:

Pre-study (within 1 month prior to treatment, including genotyping), T=0 (start hyperthermia), at start and end of plateau, after cooling, T=12 hours, T=24 hours, T=1 week, T=2 weeks, T=3 weeks, T=4 weeks, T=8 weeks, T=12 weeks, T=16 weeks, T=20 weeks, T=24 weeks.

In total HCV quantitative PCR will be performed 15 times per patient, HCV genotyping will be performed pre-study.

To study the cytokine changes after the hyperthermic treatment in conjunction with the viral load, at the same points of time, blood will be drawn to measure: serum IL-1∃ (immune response cytokine), IL-2 (immune response cytokine), IL-6 (Th2 type cellular immune response), IL-10 (Th1 type cellular immune response, polymorphism (9)), TNF-∀ (anti-viral cytokine), IFN-((anti-viral and immune stimulatory).

The intervals being; pre-study, at T=24 hours, at T=1 week, T=2 weeks, T=3 weeks, T=4 weeks, T=8 weeks, T=12 weeks, T=16 weeks, T=20 weeks, T=24 weeks also blood will be drawn to test cellular immunity to HCV.

Test can/may be:

1. Measurement of CD8 (+) HCV-specific IFN-(producing cells, as these show a correlation with HCV clearance in acute HCV infection (4, 5)

with spot-ELISA and/or tetramers conjugated with HCV antigens and/or intracellular cytokine detection for CD4 and CD8 cells.

2. Measurement of T-cell proliferation to HCV-structural (Core, E1, E2) and non-structural (NS3/4, NS5) proteins (6, 7, 8).

These methods will be tried out in the laboratory first and the optimal method (in terms of test result, feasibility) will be chosen.

During the study the immune parameter testing will be analysed and based on the results, a decision will be made whether or not to continue with the testing.

Within the 12 months pre-study period, the patient will undergo a liver biopsy. The sample of liver tissue obtained will be investigated for histology (Pathology department) as well as by PCR with HCV-specific primers and by DNA-hybridisation with HCV-specific probes. 6 months after the treatment another biopsy will be taken (providing informed consent has been obtained) to investigate the same parameters.

All parameters are shown in the flow chart. The results will be analysed statistically with ANOVA as independent parameters and also in relation with each other in a multi-factorial analysis.

Flow chart ancillary study protocol

	T=pre	T=pre	T=0	T=2 hours	T=4 to 6 hours	T= 8 hours	T=24 hours	T=1 week	T=2 weeks	T=3 weeks	T=4 weeks	T=8 weeks	T=12 weeks	T=16 weeks	T=20 weeks	T=24 weeks
	-12 to 0 month	-2 to 0 month	Start hyper-thermia	During hyper-thermia	After hyper-thermia											
Liver biopsy	X															
HCV-QRNA		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Genotype HCV		x														
IL-1∀/ ∃			x	x	x	x	x	x	x	x	x	x	x	x	x	x
IL-2			x	x	x	x	x	x	x	x	x	x	x	x	x	x
IL-6			x	x	x	x	x	x	x	x	x	x	x	x	x	x
IL-10			x	x	x	x	x	x	x	x	x	x	x	x	x	x
IFN-∀			x	x	x	x	x	x	x	x	x	x	x	x	x	x
IFN-(			x	x	x	x	x	x	x	x	x	x	x	x	x	x
TNF-∀			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cellular immunity		x					x	x	x	x	x	x	x	x	x	x

Device Description

The device used in the Clinical Protocol is the TEMET™ System. The TEMET™ System is composed of three (3) main components: TEMET™ System 1000 Console, TEMET™ System heater-cooler, and TEMET™ System 1000 TransPak™ Blood Circuit. All of these components are available from First Circle Medical, Minneapolis, Minnesota.

The TEMET™ System 1000 incorporates a console, a heater-cooler, a blood circuit and temperature probes used for the induction and monitoring of the hyperthermia procedure. The console contains the drive motor, motor controller and electronics for monitoring system parameters (temperature, pressure and flow). The TEMET™ System 1000 heater-cooler is used to supply heated or cooled water to the heat exchanger located in the TEMET™ System 1000 TransPak™ Blood Circuit. If heated water is circulated through the heat exchanger, the desired effect is to elevate the patient's blood temperature. If cool water is circulated through the heat exchanger, the desired effect is to reduce the patient's blood temperature.

The sterile disposable blood contact circuit (TEMET™ System 1000 TransPak™ Blood Circuit) is comprised of components for inducing and monitoring hyperthermia. In order to complete the circuit, vascular access is required. Blood leaves the patient via a venous cannula and PVC tubing, which directs blood to a centrifugal pump. From the pump, the blood is propelled through the heat exchanger where thermal exchange occurs, with the assistance of the heater-cooler. After the blood is heated it passes through a blood filter before returning to the patient via a second venous cannula. A calibrated thermistor probe placed within the outlet of the heat exchanger monitors circuit temperature. This position will represent the highest blood temperature reading in the circuit. The patient temperatures and the temperatures recorded from the blood circuit and the heater-cooler water bath will be the basis of the circuit operator management.

Circuit flow is measured by an electrically isolated electromagnetic flow meter built into the console, and a flow insert that is located in the blood circuit. Once a venovenous circuit is established, flow is initiated through the circuit. Flow should not exceed 5% of patient's assessed resting cardiac output until integrity of circuit is established. Once circuit integrity is established flow is increased so as not to exceed 20% of assessed resting cardiac output (average

cardiac output is between 5 to 6.5 L per minute). Blood flow rate adjustment can be used with water bath temperature adjustment to fine tune the process and maintain the core body temperature within a narrow range for the appropriate time.

Circuit pressure monitoring is accomplished by the pressure electronics built into the console and a transducer, which is located at the input side of the heat exchanger. This position, within the circuit, allows the operator to monitor resistance to flow downstream of the pump. Changes in the pressure reading can be used as a diagnostic tool to determine circuit integrity.

The TEMET™ System 1000 Console and the TEMET™ System heater-cooler have been tested and have passed all applicable international safety standards and are qualified for CE Mark. The TEMET™ System 1000 heater-cooler selection is based on ability to meet required specification, safety and durability standards.

The TEMET™ System 1000 TransPak™ Blood Circuit is designed to circulate the patient's blood by means of a centrifugal pump to a heat exchanger that heats the patient's blood to the desired parameters through a blood filter and a flow sensor then returns the heated blood to the patient. The circuit is connected to the patient via 2 cannulae each placed in the patient's greater femoral venous system at the groin region. The use of a centrifugal pump provides the necessary pressure (between 250 and 300 mmHg) to efficiently pump the blood while using less pressure than a peristaltic pump (3000 to 5000 mmHg), which could potentially damage blood cells. Because of the low-pressure capability, about ¼ of the blood circuit burst pressure, the risk of circuit rupture and the possible contamination to the operator or blood loss to the patient is greatly reduced. The TEMET System TransPak™ Blood Circuit and its components have been tested for biocompatibility and will be provided "Sterile" to the end user. In addition, the TransPak™ Blood Circuit will be labeled "For Single Use Only" as to prevent the possible cross contamination between patients or to health care workers coming in contact with the device.

Computerized controls can be added to all of the equipment described above.

The above description is provided for the purpose of describing embodiments of the invention and is not intended to limit the scope of the invention in any way. It will be apparent to those skilled in the art that various

modifications and variations can be made without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

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What is claimed is:

1. A method for treating a patient having a level of steatosis comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to reduce the patient's level of steatosis by 30 percent or more six months after the core temperature has been raised and returned to normal at least one time, and wherein the patient's level of steatosis is determined at least once before the core temperature has been raised said at least one time.

2. The method of claim 1, wherein the core temperature of the patient is raised and returned to normal one time.

3. The method of claim 1, wherein the core temperature of the patient is raised and returned to normal two or more times.

4. The method of claim 1, wherein the core temperature is raised by circulating the patient's blood from the patient, through an extracorporeal blood flow circuit, and back to the patient, wherein the blood returned to the patient has been heated within the blood flow circuit to an elevated temperature range.

5. The method of claim 4, wherein the patient's blood is circulated from the patient through a blood vessel and returned to the patient through a blood vessel.

6. The method of claim 4, wherein the patient's blood is circulated from the patient through a vein and returned to the patient through a vein.

7. The method of claim 4, wherein the patient's blood is circulated from the patient through an artery and returned to the patient through a vein.

8. The method of claim 1, wherein the core temperature is raised by inserting a heating element into the patient and wherein the heating element heats the patient's blood.

9. The method of claim 8, wherein the heating element is inserted into a blood vessel of the patient.

10. The method of claim 1, wherein the core temperature is raised to a temperature range of from 38 to 43°C.

11. The method of claim 1, wherein the core temperature is raised to a temperature range of from 41 to 42°C.

12. The method of claim 10, wherein the core temperature is measured rectally.

13. The method of claim 10 or 11, wherein the core temperature is raised for a period of from 2 minutes to sixteen hours.

14. The method of claim 10 or 11, wherein the core temperature is raised for a period of from one-half to three hours.

15. The method of claim 10 or 11, wherein the core temperature is raised for a period of from one to two hours.

16. The method of claim 10 or 11, wherein the core temperature is raised for a period of from 100 to 140 minutes.

17. The method of claim 1 or 4, wherein the patient's level of steatosis is determined at least once after the core temperature has been raised and returned to normal said at least one time.

18. The method of claim 1 or 4, wherein the patient's level of steatosis is reduced by 50 percent or more six months after the core temperature has been raised and returned to normal said at least one time.

19. The method of claim 1 or 4, wherein the patient's level of steatosis is reduced by 75 percent or more six months after the core temperature has been raised and returned to normal said at least one time.

20. The method of claim 1 or 4, wherein the patient's level of steatosis is reduced by 90 percent or more six months after the core temperature has been raised and returned to normal said at least one time.

21. The method of claim 1 or 4, wherein the patient's level of steatosis is reduced by 95 percent or more six months after the core temperature has been raised and returned to normal said at least one time.

22. The method of claim 1 or 4, wherein the patient's level of steatosis is eliminated six months after the core temperature has been raised and returned to normal said at least one time.

23. The method of claim 1 or 4, wherein the patient has macrovesicular steatosis.

24. The method of claim 1 or 4, wherein the patient has microvesicular steatosis.

25. The method of claim 1 or 4, wherein the patient has macrovesicular and microvesicular steatosis.

26. The method of claim 1 or 4, wherein the patient has macrovesicular steatosis and the macrovesicular steatosis is eliminated six months after the core temperature has been raised and returned to normal said at least one time.

27. The method of claim 1 or 4, wherein the patient has microvesicular steatosis and the microvesicular steatosis is eliminated six months after the core temperature has been raised and returned to normal said at least one time.

28. The method of claim 1 or 4, wherein the patient has macrovesicular and microvesicular steatosis and the macrovesicular and microvesicular steatosis are eliminated six months after the core temperature has been raised and returned to normal said at least one time.

29. The method of claim 1 or 4, wherein the patient is infected with hepatitis C virus.

30. The method of claim 1 or 4, wherein the patient is not infected with hepatitis C virus.

31. The method of claim 1 or 4, wherein the patient is infected with hepatitis B virus.

32. The method of claim 1 or 4, wherein the patient is not infected with hepatitis B or C virus.

33. The method of claim 1 or 4, wherein the patient is obese.

34. The method of claim 1 or 4, wherein the patient has diabetes mellitus.

35. The method of claim 1 or 4, wherein the patient has malabsorption.

36. The method of claim 1 or 4, wherein the patient has been exposed to steroids.

37. The method of claim 1 or 4, wherein the patient has steatohepatitis.

38. The method of claim 1 or 4, wherein the patient has non-alcoholic and non-viral steatohepatitis.

39. The method of claim 1 or 4, wherein the patient has viral steatohepatitis.

40. The method of claim 1 or 4, wherein the patient has alcoholic steatohepatitis.

41. The method of claim 1 or 4, further comprising treating the patient with a pharmaceutical indicated for hepatitis C.

42. The method of claim 1 or 4, further comprising treating the patient with a pharmaceutical indicated for steatosis.

43. A method for treating a patient having a level of steatosis comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to reduce the patient's level of steatosis by 30 percent or more three months after the core temperature has been raised and returned to normal at least one time, and wherein the patient's level of steatosis is determined at least once before the core temperature has been raised said at least one time.

44. The method of claim 43, wherein the core temperature of the patient is raised and returned to normal one time.

45. The method of claim 43, wherein the core temperature of the patient is raised and returned to normal two or more times.

46. The method of claim 43, wherein the core temperature is raised by circulating the patient's blood from the patient, through an extracorporeal blood flow circuit, and back to the patient, wherein the blood returned to the patient has been heated within the blood flow circuit to an elevated temperature range.

47. The method of claim 43, wherein the core temperature is raised to a temperature range of from 38 to 43°C.

48. The method of claim 43, wherein the core temperature is raised to a temperature range of from 41 to 42°C.

49. The method of claim 43 or 46, wherein the patient's level of steatosis is determined at least once after the core temperature has been raised and returned to normal said at least one time.

50. The method of claim 43 or 46, wherein the patient's level of steatosis is reduced by 50 percent or more three months after the core temperature has been raised and returned to normal said at least one time.

51. The method of claim 43 or 46, wherein the patient's level of steatosis is reduced by 75 percent or more three months after the core temperature has been raised and returned to normal said at least one time.

52. The method of claim 43 or 46, wherein the patient's level of steatosis is reduced by 90 percent or more three months after the core temperature has been raised and returned to normal said at least one time.

53. The method of claim 43 or 46, wherein the patient's level of steatosis is reduced by 95 percent or more three months after the core temperature has been raised and returned to normal said at least one time.

54. The method of claim 43 or 46, wherein the patient's level of steatosis is eliminated three months after the core temperature has been raised and returned to normal said at least one time.

55. The method of claim 43 or 46, wherein the patient has macrovesicular steatosis and the macrovesicular steatosis is eliminated three months after the core temperature has been raised and returned to normal said at least one time.

56. The method of claim 43 or 46, wherein the patient has microvesicular steatosis and the microvesicular steatosis is eliminated three months after the core temperature has been raised and returned to normal said at least one time.

57. The method of claim 43 or 46, wherein the patient has macrovesicular and microvesicular steatosis and the macrovesicular and microvesicular steatosis

are eliminated three months after the core temperature has been raised and returned to normal said at least one time.

58. A method for treating a patient having a level of steatosis comprising raising the temperature of the patient's liver and then returning the temperature of the patient's liver to normal at least one time, wherein the temperature of the patient's liver is raised to a temperature range and a duration sufficient to reduce the patient's level of steatosis by 30 percent or more six months after the temperature of the patient's liver has been raised and returned to normal at least one time, and wherein the patient's level of steatosis is determined at least once before the temperature of the patient's liver has been raised said at least one time.

59. The method of claim 58, wherein the temperature of the liver is raised by local, regional, or intraperitoneal hyperthermia.